

Policy #: 096

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Title

Pharmacogenomic and Metabolite Markers for Patients Treated with Azathioprine (6-MP)

Description

Azathioprine (AZA) is an immunosuppressant drug which is very effective for treatment of inflammatory bowel disease, particularly in patients who do not respond to steroids. AZA is known as a pro-drug, meaning that AZA itself is not the active chemical, but is metabolized (chemically changed) by enzymes (which are proteins that serve as facilitators, or catalysts, for chemical reactions) into chemical compounds that are active immunosuppressant agents. AZA is converted to two different active compounds, known as metabolites, by two distinct enzymes.

While these metabolites are very effective in treating inflammatory bowel disease, they both have toxic side effects, one causing damage to the liver, the other inhibiting the production of white cells and antibodies, thus impairing the immune system. In a small number of patients, however, the enzyme that produces the metabolite causing hepatotoxicity is absent or present in very low amounts. In these patients, taking AZA will produce excessive amounts of the other metabolite, which causes bone marrow suppression and may lead to life-threatening infections. These patients should either not take AZA, or take it in a reduced dosage, depending on whether there is no enzyme or a low enzyme level.

The two enzymes that metabolize AZA are produced from genes in the nucleus of cells in the body. Everyone has two copies of every gene. However, patients who have low levels of one of the enzymes have one defective gene (known as a mutation) and one good copy. Patients who have no level of one of the enzymes have two defective copies. Using new technology, it is now possible to analyze these genes once prior to starting AZA therapy to see if there are defective genes present. This is known as genotyping. Patients who have only one good copy could be started on AZA, but at a much lower dose, and patients who have no good copies should not be treated with AZA. Genotyping has been found to be effective in identifying patients who are at increased risk for toxicity from AZA. Alternatively, the activity of the enzymes that convert AZA into its metabolites could be measured. This would be considered a phenotypic test.

Another suggested approach to avoiding bone marrow suppression from AZA is to measure the metabolites of AZA directly. Ranges could be established that correlate with effectiveness, and excessive buildup of toxic metabolites could be detected and dosing adjusted. There have been no randomized controlled clinical trials that demonstrate the effectiveness of this approach.

When services are covered for all Products (including Medicare HMO Blue, Medicare PPO Blue and Blue Medicare PFFS PlusRx)

We cover either genotypic analysis of the TPMT (thiopurine methyltransferase) gene **or** phenotypic analysis of TPMT enzymatic activity for the management of inflammatory bowel disease when at least one of the following indications is present:

- Prior to initiation of azathioprine or 6-mercaptopurine therapy; or
- In patients on azathioprine or 6-mercaptopurine therapy with abnormal complete blood count (CBC) results that do not respond to dose reduction.

Note: Only one or the other of the genotype or phenotype tests is considered medically necessary when either of the above indications is met.

When services are not covered for all Products (including Medicare HMO Blue, Medicare PPO Blue and Blue Medicare PFFS PlusRx)

We do not cover analysis of the metabolite markers of azathioprine and 6-mercaptopurine (6-MP), including, but not limited to, 6-methyl-mercaptopurine nucleotide (6-MMPN) and 6-thioguanine nucleotide (6-TGN), for all indications.

Individual consideration

All our medical policies are written for the majority of people with a given condition. Each policy is based on medical science. For many of our medical policies, each individual's unique clinical circumstances may be considered in light of current scientific literature. For consideration of an individual patient, physicians may send relevant clinical information to:

For services already billed

Blue Cross Blue Shield of Massachusetts
Provider Appeals
PO Box 986065
Boston, MA 02298

Prior to performance of service

Blue Cross Blue Shield of Massachusetts
Case Creation/Medical Policy
One Enterprise Drive
Quincy, MA 02171
Tel: 1-800-327-6716
Fax: 1-888-641-5330

Managed care guidelines

Authorizations are not required if performed in an outpatient setting
All specialist visits require a referral

Indemnity and PPO guidelines

Authorizations are not required if performed in an outpatient setting

Coding information

Procedure codes are from current CPT, HCPCS Level II, Revenue Code, and/or ICD-9-CM manuals, as recommended by the American Medical Association, Centers for Medicare and Medicaid Services and American Hospital Associations. Blue Cross Blue Shield Association national codes may be developed when appropriate.

The following codes are included below for informational purposes. Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

There is no specific code for genotypic analysis of TPMT or phenotypic analysis of TPMT enzymatic activity.

According to the laboratories offering this testing, they use a combination of the CPT codes listed below to code for this test (for example, Prometheus uses 83891, 83898 x3; 83896 x6; 83912):

Molecular Diagnostic CPT codes:

- **83890:** Molecular diagnostics; molecular isolation or extraction
- **83891:** isolation or extraction of highly purified nucleic acid
- **83892:** enzymatic digestion
- **83896:** nucleic acid probe, each
- **83898:** amplification, target, each nucleic acid sequence

- **83900:** amplification, target, multiplex, first two nucleic acid sequences
- **83909:** separation and identification by high resolution technique (e.g., capillary electrophoresis)
- **83912:** interpretation and report
- **83914:** Mutation identification by enzymatic ligation or primer extension, single segment, each segment (e.g., oligonucleotide ligation assay [OLA], single base chain extension [SBCE] or allele-specific primer extension [ASPE])

Genetic Testing code modifier:

9A - TPMT, commonly called thiopurine methyltransferase (patients on antimetabolite therapy)

HCPCS Level II codes:

- **J7500,** Azathioprine, oral, 50 mg.
- **J7501,** Azathioprine, parenteral, 100 mg.
- **S0108,** Mercaptopurine, oral, 50 mg.

Note: These services are not covered when the above noted criteria are not met.

Definitions

Genotypic analysis: a laboratory test that looks at the genetic makeup of target genes, including analysis of variations or mutations that may predict or indicate a particular trait or clinically significant condition.

Phenotype: a specific manifestation of a trait, such as size, eye color, or behavior that varies between individuals. Phenotype is determined to some extent by genotype, or by the identity of the alleles that an individual carries at one or more positions on the chromosomes. Many phenotypes are determined by multiple genes and influenced by environmental factors

Metabolite: any substance produced by metabolism or by a metabolic process

Pharmacogenomics: is the branch of pharmacology which deals with the influence of genetic variation on drug response in patients by correlating gene expression or single-nucleotide polymorphisms with a drug's efficacy or toxicity. Pharmacogenomics aims to develop rational means to optimise drug therapy, with respect to the patients' genotype, to ensure maximum efficacy with minimal adverse effects. Such approaches promise the advent of "personalized medicine"; in which drugs and drug combinations are optimised for each individual's unique genetic makeup. Pharmacogenomics is the whole genome application of pharmacogenetics, which examines the single gene interactions with drugs.

TPMT: (Thiopurine s-methyltransferase) Test for the detection of patients who are at risk of developing severe side effects if treated with the thiopurine drugs such as the most commonly used thiopurine drug, azathioprine.

Policy update history

New Policy, effective 5/09

Footnotes

¹Based upon New BCBSA national policy 2.04.19, issued 8/08.

References

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